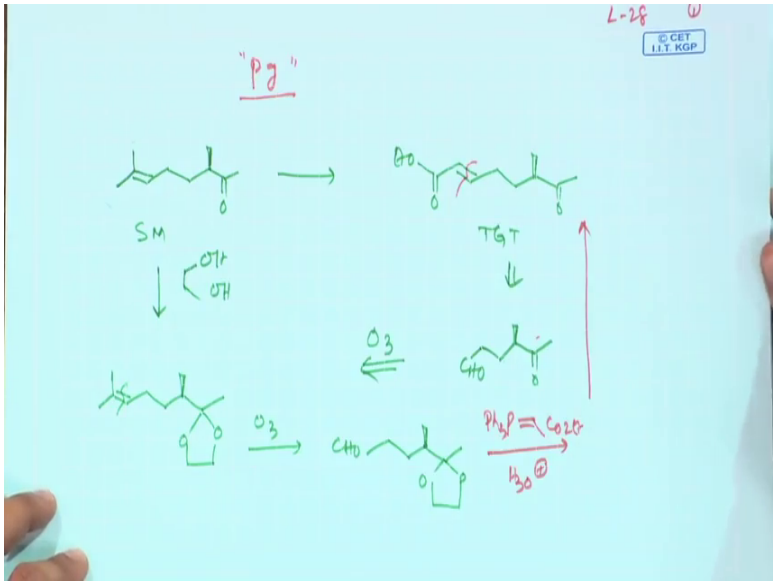
A Study Guide in Organic Retrosynthesis: Problem Solving Approach

Prof. Samik Nanda
Department of Chemistry
Indian Institute of Technology, Kharagpur

Lecture – 28
Fg based Strategy (Contd.)

So welcome back students, we basically discussing functional group based strategies and we are mainly focusing on several protecting groups, and how these protecting groups can be selectively protected as well has deprotected.

(Refer Slide Time: 00:27)



Now this particular week we will be talking about some example, where you find that how you can use couple of protecting groups for doing sums in three transformations. The first program which I am giving, a starting material was given to you, starting material was given to you and the target which was desired is having this structure.

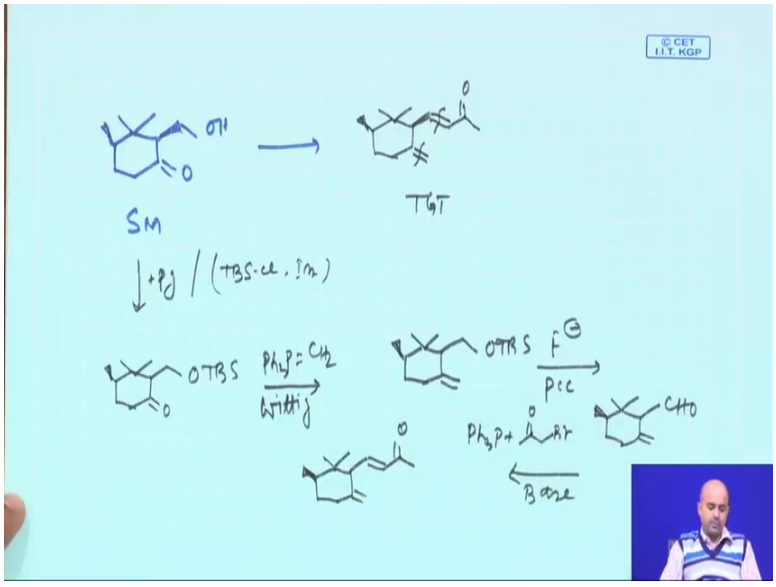
Let me see the starting material and the target and do a close analysis in a retrosynthetic way and find that only thing is, the left hand side, this Olefinic bond needs to be reformed. It is basically two methyl groups have been removed in place of a alpha beta unsaturated rester, this is a target molecule. So, what will I do? I will try to do a retro by keeping remaining all things intact, using that this retro would be doing by keeping this bond by using a CH 2 CH 2 CH o by using a wittig reaction. So, if you have a wittig kind of reaction, you can basically easily can do it. Now correlate this to compound, the

starting material is this. So, if you are doing a oxidative cleavage of this double bond you can easily clave it. Now if you have this compound, this compound is what. This compound is keto as well as aldehyde, keto and aldehyde. We are saying that this keto and aldehyde you want do a Wittig reaction to prepare this alpha beta unsaturated double bond, means that your keto or aldehyde both are basically will undergo Wittig reaction.

So, though aldehyde reaction very faster compared to keto, but the ketone needs to be protected. So, now, based on this strategy we will formulate, how we can proceed. So, initially the ketone group will be protected. The ketone group can be best protected by ethyln glycol in presence of little bit of acid. So, this ketone is now protected as it is cyclic ketal it is protected, then you do the ozonolysis. So, ozonolysis means you get the oxidic cleavage here. So, what you will get? You get this corresponding aldehyde, then your remaining part of the molecule will be same as it is. Then you are almost close.

Now you do the Wittig reaction and then you see the Wittig reaction will be now working on here, and then once Wittig reaction was done you just remove this ketal to come back to your target molecule. So, it is basically a just functional group protection, do the FGI, then protection group removal. So, that is why the protecting group also can act as a very good functional group, and you need to take care of this particular protecting group in a synthetic planning.

(Refer Slide Time: 04:32)



Next particular example we will be discussing the cyclic molecule and the structure of the starting material which was given as this starting material. The target which I am now drawing, is having something like this kind of structure, may be see the target and try to analyze with this starting material, we will find that basically you need to do a new carbon carbon bond formation here as well as this CH 2 OH, there also you need to do a carbon carbon bond forming reaction

So, one is here, one is here. So, means that basically you can think about the carbon carbon bond forming reaction by standard Wittig reaction. So, you are having a carbon is already there and you are having CH 2 OH, and if you initially do a oxidation kind of thing on this primary alcohol without protecting it, you will basically get a keto aldehyde. The keto aldehydes, then you have a difficult scenario, because the wittig insertion of this particular groups are different. One case you need a simple methylene, one case you need a alpha beta unsaturated ketone

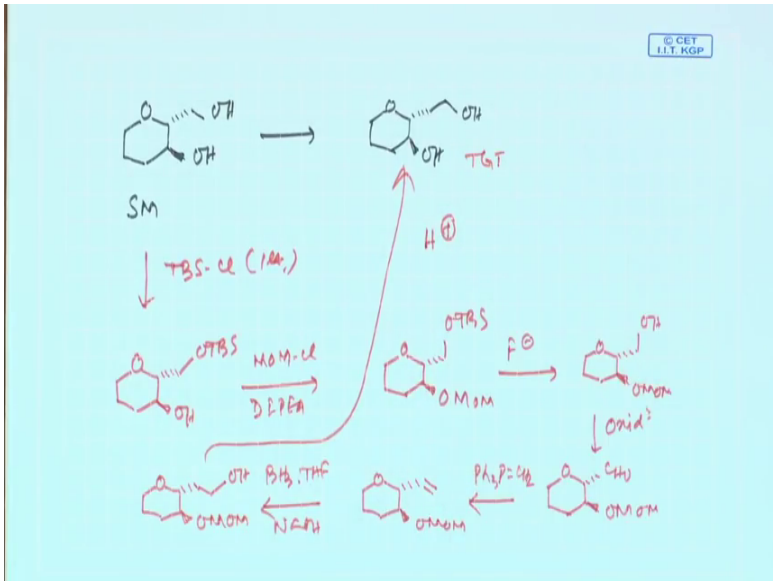
So, basically you have to rely on protecting group. Now this alcohol can be protected by numerous protection groups. You can used TBS chloride as the simple protecting group an imidazole. In principle, as I said any other protecting groups you can also use. So, that will basically give you the correspondence silyl leather, and this synil leather is now you are having a ketone, you do the one carbon wittig reaction, one carbon wittig transformation that will basically give you the exocyclic methylene group, and now wants the exocyclic methylene group is there, now next see that what you need to do next. Next basically you need to do the de protection of this silyl group, because you need to do a another carbon carbon bond forming reaction at this particular carbon.

So, F minus will remove this TBS then you do the oxidation by Pcc, then basically we will be end up in this compound CHo. Now everything is almost set you can do a Wittig reaction even you can do a aldehyde kind of reaction also, but as we discussed about wittig reaction, let us talk about a Wittig reaction with a ylide you can easily prepare from tryphenal phosphine and monobhromo acetone and use a base to complete the synthesis in a very effective way.

The only thing is, you have to use this protecting group of this alcohol. So, this three alcohol needs to be protected prior to the initial Wittig reaction. So, this kind of selective

production and deproduction is a very useful strategy for making a medium sized target as well as complex target.

(Refer Slide Time: 08:27)



The next target which will be now discussing, next problem will basically a starting material was given the tetrahydropyran based compounds starting material was given.

The target molecule which was required, is having 2 CH 2 and this part is the OH. So, basically you need a homologation, add this particular primary hydroxyl things, you need a 2 CH 2. Now you will find this compound is by having two hydroxyl primary as well as hydroxyl, and you need to do a selective FGI at the primary hydroxyl thing. So, basically you need to protect the secondary in presence of primary, but that was often bit difficult. So, what I will suggest you do it know this way, you take a first a TBS chloride one equivalent, and then basically that will give you the primary which is sterically less congested we will first protected ok.

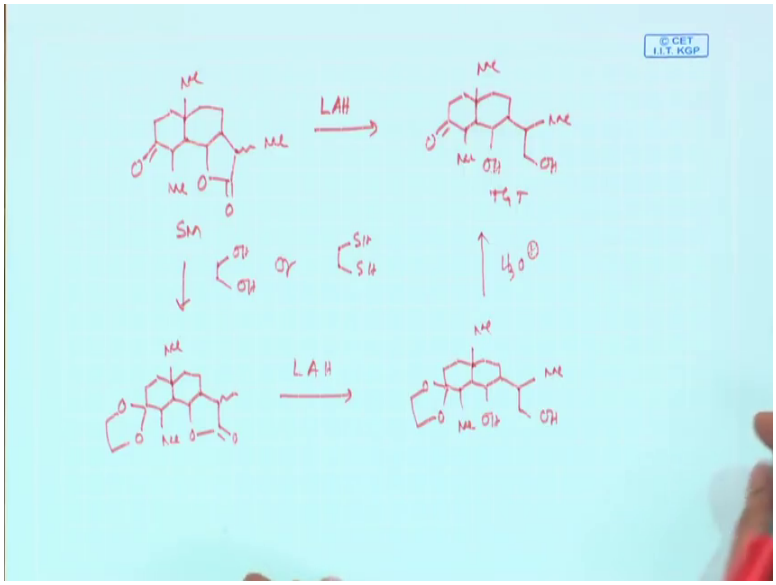
The secondary now you touch, the secondary you can touch or you can protect by different protecting groups, you can use silicon protecting groups like tertiary butyl diphenyl silyl which will not be affected when you do the assimilated deproduction of TBS. Let us say do a other chemistry, you do a MOM chloride production, MOM chloride use depea or now this secondary is now protected as is MOM and this one is now o TBS.

So, now as is the synthetic strategy requires you need to d block this particular TBS protecting group as you need to have a FGI here. So, fluoride minus is the best thing that will basically remove the silyl, and it will give you CH 2 OH. Now as you need to do a one carbon extension, the based reaction is basically a hydroboration reaction. So, for that you need to oxidized first, to convert the primary hydroxy to corresponding aldehyde, the MOM production remains same.

Now, aldehyde is subjected to next Wittig, one carbon Wittig reaction, very straight forward reaction. So, we are basically close. So, one carbon extension was almost done, now you do a hydroboration reaction BH 3 THF sodium hydroxide. Once you do the hydroboration, you basically get CH 2 CH 2 OH, and this MOM is there. Now you try to remove this MOM groove by some acid catalyst, and that will basically give you the, your target molecule.

So, on this way just by using selective production and deproduction, you can basically play with the target molecule and try to correlate with the starting material that how the starting material can selectively be used or can functionally manipulate it to the given target. The next couple of problems we have similar kind of scenario, but what will try to do.

(Refer Slide Time: 12:34)



I will ask your opinion that how these functional group transformations can be effectively carried out, and what you think about the entire pathway. We have a

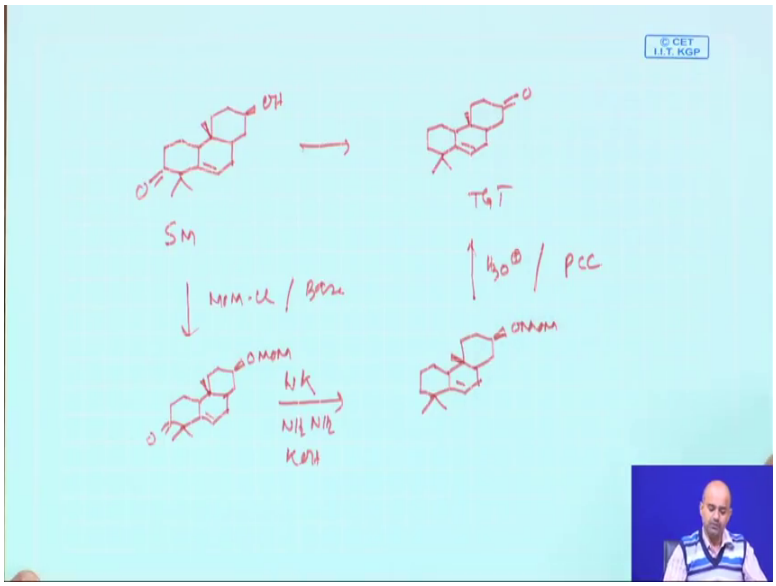
compound something like this, the stereochemistry portion I have not mentioned here, the compound structure is this. And I said if this compound I will be giving you a reagent lithium aluminium hydride, other regions I am saying that I will at present I am not going to give you and your target molecule is.

See the target molecule, the target molecule which is requested to synthesized as having structure this. Let me now closely analyzed, the starting material is this which was supplied to you and the target was sought that this molecule you have to make by using a lithium aluminum hydride reduction I have given you.

Let me see this compound contains stating material currents a ketone as well as a lactone or cyclic ester. If you know subject this compound, the starting material itself with LH lactone will definitely be reduced to give you the diol as desired, the same time the ketone will be also reduced, but which is essentially it not required. So, means that here initially the ketone groups needs to be protected. The ketone group protection as all of us are familiar; you can do a 1 2 ethylene glycol protection or even you can do a 1 2 thiol protection, depending on the availability of the reagent, you can basically protect this to thiol or corresponding oxygen analog. The other part of this molecule will remain similar. Now as the ketone has been protected, now the ketone is basically is reactivity has been suppressed, now you to have subject it to lithium aluminium hydride.

Now see this lactone will be reduced as LAH is very strong reducing agent, and then you will basically get this diol which is the diol core functionality was present in the target molecule, the protecting group remains same and then if you just remove the protecting group by acidic workup, will basically end up with this final product. So, this kind of strategy which basically gives you idea that where and which point you do not use the protecting group, it is basically tricky, but you need to be very careful when you do such kind of exercise.

(Refer Slide Time: 16:25)



The next one will be on similar thought, will be basically talking about a cyclic molecule and this is the cyclic molecule structure is this, starting material was this. The target which was needed or which we need to synthesize from this molecule say double bond does not matter, and then that target which basically you need to make, yes this ketone. The starting material, if you see the starting material starting material is having a ketone and a hydroxyl group.

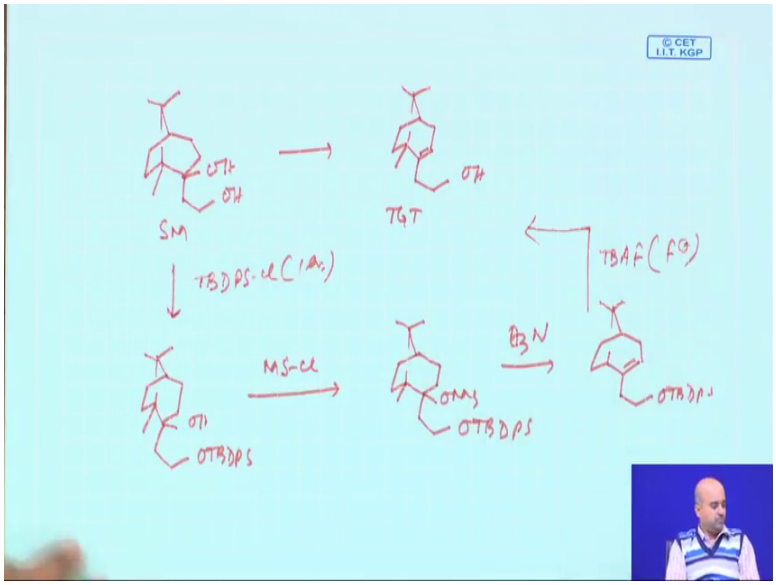
The final target the ketone has been deoxygenated, a basically is a kind of redundant functionality, and then this end of this molecule is now oxidized, this hydroxyl group is oxidized. So, basically you need to do two reactions, you need to selectively do a deoxygenation here as you need to do a oxygenation or oxidation particularly at this carbon. Now let us initially try that what kind of reaction you can think about.

Now, in principle if you first oxidize this molecule with a suitable oxidizing agent that will give you a diketone, now one of the diketone has been generated you have a difficulties for selective deoxygenation of diketones, because this end this ketone you need to be deoxygenated. So, basically at the very beginning you protect with this OH group. Let us say protect with MOM chloride, MOM chloride and a base depea. So, initial protection, the all the structural features of the remaining part will be similar reported to it o MOM, and then this ketone it should be deoxygenated, the standard reduction like Wolff Kishner. So, basically you treat with hydrogen hydrate, this

transformation we have already discussed many times, and Wolff Kishner will basically deoxygenated, the carbonyl group and you can get this intermediate without any difficulties.

Now, what you have to do, basically need to remove this MOM group. So, which can be clipped by simple acidic workup and then we just oxidize it with a suitable oxidizing agent, that pyridinium chloro climate, and then will find that will basically end up with this particular target molecule which was desired. So, there are two simple functional groups was there, and he basically protect this hydroxy group it is MOM first, do the FGI here and then remove the MOM production group, and they knew oxidize we achieved the target. This was the very simple demonstration of a protecting group chemistry.

(Refer Slide Time: 20:06)



So, we will try to have more problem which you also can be fitted in the same line. The compound is basically having a bicyclic breached by cycles and then as a 1 3 diol. this is a 1 3 diol. Now is if the target about this is starting material which was given to you. The target molecule which was required at this stage, you put a double bond here; yes.

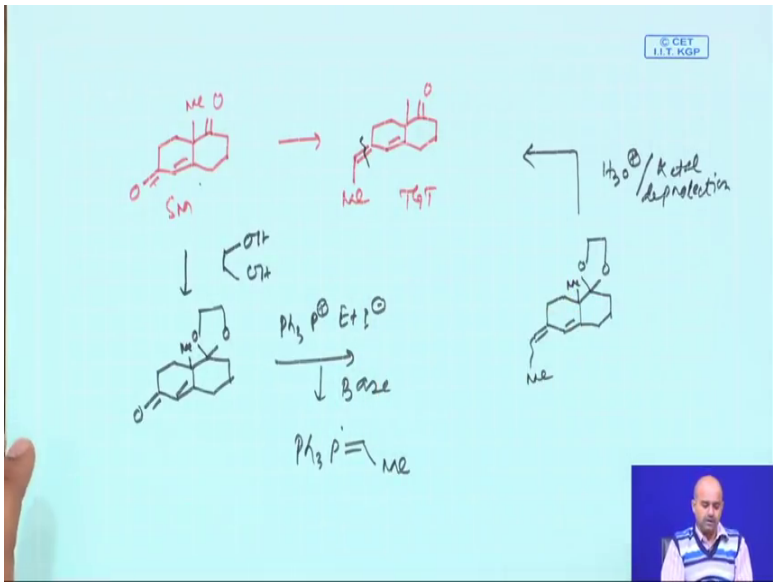
If you see the close structural viewpoint of this target and do a skeletal analysis, skeletal based analysis you find that, if you just simply do a elimination here that will give you the required double bond. Elimination can only takes place here, because there is no hydrogen. Even hydrogen is also there, the elimination on takes place, because I have to give you a double bond in the bridge position which is violating the blades rule.

So, now, there are two hydroxyls; one is tertiary, one is primary. Now if you directly try to eliminate this compound this primary OH also undergoing elimination, is because there are a hydrogens which can be easily obstructed. So, means that this primary hydroxyl group is be selectively protected.

Now, say if you having a primary, secondary, tertiary, primary hydroxyl group as sterically less in that. So, you have a efficiently you can block or you can protect the primary hydroxy group. The best way you can just now protect with, let us say the bulky protecting group is a TBDPS cl 1 equivalent definitely, and then what will be having, you will basically having, this is your OH and this is your CH 2 CH 2 or TBDPS. Now this tertiary alcohol you need to touch first convert this tertiary to corresponding mesylate which will basically give you the mesylate derivatives, because mesylate derivatives are easy to be eliminated right, convert to o mesylate, and then you heat with a base, suitable base. So, this undergoes E 2 elimination and there basically you will find the olefin.

Now, this olefin and if you analyze this target are basically very close, only thing is you need to remove this TBDPS, that you can easily do by treating with attribute aluminium fluoride, puts a nice fluoride source you can get a target molecule. So, based on the structure of this particular product, which was desired, you can efficiently design a pathway which will be very useful and very much valuable.

(Refer Slide Time: 23:53)



We will try to stop our discussion just by talking about this example and let us see this example say bicyclic ketone, but there are two, carbonyl functionality, one is alpha beta unsaturated, one is saturated. And then the target molecule which was given here, yes something like this. So, this starting material, the target now see the starting material and target would basically find that only reaction which we need to do just a wittig kind of reaction. Now if you simply do a Wittig reaction on this target, the saturated ketone might react faster, because the saturate the ketone is; obviously, very much reactive. Saturated ketone,this ketone needs to be protected at the very beginning; that is why. So, first use a simple iterative glycol which will basically protect or block your saturated counterpart.

Saturated ketone portion will be basically blocked, and then you see next what it can be done. Next basically what we need to do. You basically need to do a Wittig reaction with the help of a simple wittig ylide. Now this wittig ylide can be efficiently generated with the help of Ph 3 P plus Et i minus, triphenylphosphine ethyl iodide can simply be mixed together and you get this corresponding ylide. This ylide when you react to with a base at the beginning you basically get the. This is basically salt you basically get the corresponding ylide here, and then do the Wittig reaction which will basically now give you the double bond geometry I have not mentioned here, and then this ketal will be as it is.

Now, if you see you need to d block the ketal. You need to d block the ketal means you just react to it H 3 o plus acidic workup which will remove the ketal I say, ketal deprotection. So, ketal group is now deprotected and definitely you can end up with the final target molecule.

The only thing is the two starting material having a virtually rate differences for the initial protection; saturated carbonyl compound and unsaturated carbonyl compound. Saturated carbonyl compound is much more reactive, because for unsaturated carbonyl compound the electronic nature is little bit different due to this particular resonance, but this compound will react faster with this etheren dycol, and it will give you the cyclic ketal. So, this reactivity is suppressed, then you do the Wittig reaction or this region and you will end up with this particular target molecule.

So, similar kind of problems basically can be tackled with relatively easier functional group operation, and you need to just use selective production and deproduction group chemistry. So, production group chemistry probably we can conclude, and so guideline 4 in the functional group based strategies we have covered and try to remember there will be couple of assignments when you talk about the more production group chemistry's. And so you have to go to the assignments and please try to solve to the assignments and till then goodbye, have a good time.